Docket No. ORT-1583

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Carlos R. Plata-Salaman, et al.

Serial No.: 10/081,713 Art Unit: 1614

Filed: 2/21/2002 Examiner: Spivack, Phyllis G.

For: Carbamate Compounds for Use in Preventing or Treating Anxiety Disorders

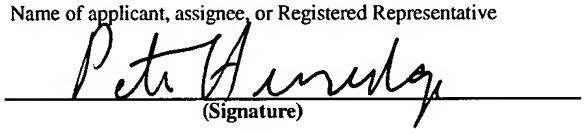
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on

November 23, 2004

(Date)

Peter L. Herridge (Reg. No. 42,658)

Name of applicant, assignee, or Registered Representative



(Signature)

November 23, 2004

(Date of Signature)

Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF BOYU ZHAO, M.D. Ph.D. UNDER 37 C.F.R § 1.132

I, Boyu Zhao, declare as follows:

1) I am a citizen of the United States and hold the position of Senior Scientist, CNS/Drug Discovery at Johnson & Johnson Pharmaceutical Development L.L.C ("J&JPRD") in Spring House, PA

2) I did my medical studies at the Capital University of Medical Sciences (CUMS), China where I received a M.D. degree in 1984. I did my graduate studies in

neurobiology and anatomy at the University of Rochester, Rochester, NY where I received a Ph.D. degree in 1994.

3) Since completing my studies, I have held the following positions:

1997 – Present	The R.W. Johnson Pharmaceutical Research Institute	
	Spring House, PA	
	2000 – Present	DD Liaison, 369 CDT/Development
	2001 – Present	Senior Scientist, CNS/Drug Discovery
	1997 – 2000	Scientist, CNS/Drug Discovery
1994 - 1997	National Institutes of Health	
	Bethesda, MD	
	1996 - 1997	Senior Staff Fellow, Molecular Genetics/NINDS
	1994 - 1996	Postdoctoral Fellow, Molecular Neurobiology/NIA
1989 - 1994	University of Rochester	
	Rochester, NY	
	1989 - 1994	Grad. Research and Teaching Assistant
1984 - 1989	CUMS/Beijing the 6th Hospital	
	Beijing, China	
	1984 - 1989	Instructor, Neurobiology
		Physician, Internal Medicine

4) I am a member of the Society for Neuroscience and the American Association for the Advancement of Science. I have published over 17 papers in peer-reviewed journals and made 27 presentations or presented abstracts at scientific symposia and conferences. I am inventor or co-inventor on 16 patent applications.

5) I am fluent in the English language. I have read and understood the specification and claims of United States Patent Application Number 10/81,713 and the Office Action (Final Rejection) mailed on September 9, 2004.

6) As part of my duties at J&JPRD, I help to design, coordinate and analyze the results of pre-clinical studies on test compounds under development. This includes investigating the effects of the present test compound on the aggressive behavior induced by isolation and the general behavior of mice. I was the

responsible co-investigator (along with Barry Dubinsky, PhD) for a study testing the effects of the test compound on the aggressive behavior in mice.

7) The report of the study issued on November 18, 2002. The test compound used in this report is the same as that shown in the specification of patent application No. 10/081,713 on page 14 as Formula (Ib) and is claimed in claims 18 and 19. As discussed in detail below, data from the experiment showed that the test compound administered at doses of 40-mg/kg p.o. inhibited isolation-induced aggressive behavior in pairs of mice tested one hour after administration. This anti-aggressive effect of the test compound was not related to sedation. In my opinion the pharmacological effect shown by the test compound in inhibiting isolation induced aggression in this animal model suggests that this compound would have an effect on aggressiveness in humans and could improve impulse control and therefore is likely to be a treatment for the broad spectrum of impulse control disorders (ICDs) in humans

8) The effects of test compound on the aggressive behavior of Crl:CD-1(ICR)BR albino mice were evaluated using the paradigm of isolation-induced aggression. Test compound at 40-mg/kg p.o. statistically significantly inhibited isolation-induced aggressive behavior in pairs of mice tested 1 hour after administration ($p < 0.05$). Test compound at 20-mg/kg p.o. also significantly shortened the onset of initiation of fighting in the treated group compared to the corresponding vehicle-treated group 4 hours after administration. The effects of test compound on general behavior were evaluated by visual observation using a checklist of behaviors. No behavioral or physical signs were observed in mice administered test compound at doses up to 100 mg/kg p.o., the test compound, administered at 300 mg/kg p.o., produced sedation.. Results suggest that the anti-aggressive activity of test compound at 40 mg/kg p.o. is not related to sedation.

9) Male Crl:CD-1(ICR)BR albino mice, fasted overnight, were individually housed for 5 weeks in plastic cages on wood-chip bedding. Subsequently, they were paired for 1 minute daily for several days by placing one

individually housed mouse (intruder) into the resident cage of another individually housed mouse (resident). The 1-minute pairing of intruder and resident mouse elicits aggressive behavior. Pairs of mice showing consistent aggressive behavior when paired for 1 minute, during several days were selected as subjects for drug testing. Test compound (10 to 40 mg/kg p.o.) or the vehicle (methocel; aqueous 0.5%, w/v, hydroxypropyl methylcellulose solution) was administered (10 mL/kg) to the resident and intruder mouse. One and 4 hours after dosing, the mice were paired and the onset of fighting was recorded. Pairs of mice that did not fight within 1 minute were separated. The duration of fighting during a 1-minute test period was recorded. Mice were re-used in this procedure after several days to a week to allow metabolism and elimination of test compounds. The mice weighed 32 to 49 g at the time of testing and were fasted overnight before dosing. Mice were euthanized with CO2 if they were sick or injured.

10) Results were expressed as the median onset of fighting and median duration of fighting in vehicle and drug-treated groups. The statistical significance of an increase in the median onset or a reduction in the median duration of fighting in pairs of mice given test compound or its vehicle 1 and 4 hours after administration was determined using the nonparametric Wilcoxon test ($p < 0.05$, 1-tailed).

11) Test compound at 40 mg/kg p.o. inhibited isolation-induced aggressive behavior in pairs of mice tested 1 hour after administration, as shown by a statistically significant reduction ($p < 0.05$; Wilcoxon rank sums, 1-tailed) in the median duration of fighting compared to that in the corresponding vehicle-treated group (See Tables 1A) When testing was repeated 4 hours after administration, the onset for initiation of fighting in the group that was administered test compound at 20 mg/kg p.o. was statistically significantly shorter than that in the corresponding vehicle-treated group. (See Table 1B) The biological significance of this reduction in onset of fighting is unclear, because the median duration of fighting was not affected in any group that was administered test compound and tested 4 hours after administration compared

to the corresponding vehicle-treated groups (See Tables 1A and 1B below).

12) In conclusion, the anti-aggressive activity of test compound at 40-mg/kg p.o. was not related to sedation, because no CNS-related effects were observed in other mice up to 4 hours after administration of test compound at 40 or 100-mg/kg p.o. although test compound at 300-mg/kg p.o. produced CNS-related effects in mice under the conditions of testing used.(See Table 2)

13) All statements made in this declaration of my own knowledge are true and all statements made on information and belief are believed to be true. All statements in this declaration are made with the knowledge that willful false statements and the like if made in this declaration are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that any willful false statement may jeopardize the validity or enforceability of any patent that may issue on the application for which this declaration is made.

Dated this 18th day of November, 2004

Boyu Zhao

Boyu Zhao, M.D. Ph.D.

TABLE 1A

EFFECT OF TEST COMPOUND ON MEDIAN ONSET AND DURATION OF ISOLATION-INDUCED FIGHTING IN PAIRS OF MICE

			1 HOUR AFTER ADMINISTRATION			
Treatment	mg/kg p.o.	N[a]	Median Onset (sec)	P	Median Duration (sec)	P
Vehicle	0	11	13	---	19	---
Test Compound	10	12	5	0.174	28	0.289
Vehicle	0	10	8	---	14	---
Test Compound	20	10	11	0.259	20	0.325
Vehicle	0	18	13	---	19	---
Test Compound	30	17	14	0.375	18	0.5
Vehicle	0	10	8	---	14	---
Test Compound	40	10	40	0.071	0.5[b]	0.035

[a] Number of pairs of mice.
[b] Compared to the vehicles treatment, run on the same day, the experimental compound produced either a statistically significant increase or decrease in onset or duration of fighting in paired mouse-isolates ($p < 0.05$; Wilcoxon rank sums, 1-tailed).

TABLE 1B

EFFECT OF TEST COMPOUND ON MEDIAN ONSET AND DURATION OF ISOLATION-INDUCED FIGHTING IN PAIRS OF MICE

			4 HOURS AFTER ADMINISTRATION			
Treatment	mg/kg p.o.	N[a]	Median Onset (sec)	P	Median Duration (sec)	P
Vehicle	0	11	34	---	2	---
Test Compound	10	12	4	0.092	6	0.366
Vehicle	0	10	50	---	12	---
Test Compound	20	10	4[b]	0.036	26	0.078
Vehicle	0	18	34	---	2	---
Test Compound	30	17	4	0.32	9.5	0.215
Vehicle	0	10	50	---	12	---
Test Compound	40	10	17	0.255	20	0.281

[a] Number of pairs of mice.
[b] Compared to the vehicles treatment, run on the same day, the experimental compound produced either a statistically significant increase or decrease in onset or duration of fighting in paired mouse-isolates ($p < 0.05$; Wilcoxon rank sums, 1-tailed).

TABLE 2

EFFECTS OF ORAL ADMINISTRATION OF TEST COMPOUND ON THE GENERAL BEHAVIOR OF MALE MICE

	Number of Mice Affected (N = 3/group) Mg/kg p.o.[a]					
	40		100		300	
Physical and behavioral signs	1 h	4h	1h	4h	1h	4h
Deceased Open Field Activity	0	0	0	0	3	2
Impaired Horizontal Screen	0	0	0	0	3	2
Performance						
Locomotor Ataxia	0	0	0	0	0	2
Soft Body Tone	0	0	0	0	3	2
Loss of Righting Reflex	0	0	0	0	3	0
Loss of Corneal Reflex	0	0	0	0	3	0
Loss of Pinnal Reflex	0	0	0	0	3	0
Extensor Limb Tone (Hindlimb)	0	0	0	0	3	2
Impaired Visual Placing Reflex	0	0	0	0	3	0
Decreased Startle Reflex	0	0	0	0	3	0
Reduced Skin Plasticity	0	0	0	0	3	0
Tail Pinch Response, Absent	0	0	0	0	3	0
Passive Response to Handling	0	0	0	0	3	0

[a] Test compound was suspended in the vehicle which consisted of 0.5%, w/v, aqueous hydroxypropyl methylcellulose, approximately 4000 cps; GFI-90000-000-E-004X, Lot 9428N.